REMARKS:

Claims 1, 6, 7, 10, 15, 18, 20, 27, 28, 56, 58 and 60 have been amended.

Claims 16, 17, 19, 25, 57, 59 and 61 have been cancelled without prejudice to their patentability, and may be reasserted in this, or another, prosecution.

Claims 34 – 55 stand withdrawn.

Claims 62 – 75 have been added.

Claims 1 – 15, 18, 20 – 24, 26 – 56, 58, 60, and 62 – 75 are now in the case.

It is believed that no new matter has been added.

Claims 1, 15 and 28 have been amended by adding the description that the reactive tricalcium phosphate nanoparticles include a sulfate salt in an amount sufficient to prevent at least a portion of the tricalcium phosphate from forming hydroxyapatite, and by deleting the phrase describing other ingredients required to form a cementous material. Support for the feature involving the presence of the sulfate salt is found in original claims 36, 37 and 55, and in the specification at least at page 9, lines 12 – 29, and in Example 1: page 20, line 6 to page 22, line 15. It is believed that deletion of the phrase describing "other ingredients" increases the clarity of what is claimed.

Claim 6 is amended to resolve a potential problem with antecedent basis by deleting the reference to the "cementous material", and by capitalizing the first letters of the term "Group", as it applies to the description of Group IA or Group IIA elements.

Claim 7 is amended to clarify that the counterion that is being described is the counterion for the carbonate salt.

Claim 10 has been amended as suggested in the Action of June 6, 2003, by replacing the terms involving "capable of curing", with the terms "which cures".

Claim 18 has been amended to correct dependency and to capitalize the first letters of the terms "Group IA and Group IIA".

Claims 20 and 23 have been amended to correct dependency.

Claim 27 has been amended by replacing the term "comprising" with --- is---.

Claims 56, 58 and 60 have been amended to describe the sulfate salt as sodium sulfate. Support for this feature can be found in the original claims and in the specification as originally filed at the locations described above for the amendment of claims 1, 15 and 28.

New claims 62, 68 and 72 mirror original claims 1, 15 and 28, except that the cement powder and cement paste are now described as curing to form a cured cement having a compressive strength that is greater than 65 MPa. Support for this feature can be found, at least in Figure 3, where a compressive strength of over 65 MPa is demonstrated, and in original claim 33, where a compressive strength of at least about 80 MPa is described. The features that are described in new claims 63 – 67, 69 – 71 and 73 – 75 find support at least in the dependent claims originally filed.

It is believed that new claims 62 – 75 describe an invention that is the same as that of the Group I claims (claims 1 – 33) that were elected for prosecution, and it is respectfully requested that these claims be examined with the claims of Group I.

Holding of restriction requirement as final.

The holding that the previously asserted restriction requirement has been made final is acknowledged.

Non-recognition of the Preliminary Amendment filed March 20, 2003.

It was not apparent from the Action dated June 6, 2003, that the Preliminary Amendment that was filed on March 20, 2003, had been entered or considered by the Examiner. A copy of that Preliminary Amendment is enclosed with this Amendment and Response.

All amendments to claims that are made in the present paper have been made with the assumption of the entrance of the Preliminary Amendment into the case. Accordingly, claim numbers, and the like, that are discussed herein, often refer to claims that were added in the Preliminary Amendment.

It is respectfully requested that the Office acknowledge receipt of the Preliminary Amendment and its entrance into the case.

Rejection of claims 1 – 33 under 35 USC §102(a) and (b) as anticipated by, or in the alternative, under 35 USC §103(a) as obvious over U.S. Patent No. 6,013,591 to Ying *et al.*, U.S. Patent No. 5,149,368 to Liu *et al.*, U.S. Patent Nos. 5,522,893 or 5,954,867 to Chow *et al.*, U.S. Patent Nos. 5,885,540, 5,571,493, 5,569,540, 5,709,742, or 5,683,667 to Fulmer *et al.*, or U.S. Patent Nos. 5,496,399 or 5,683,496 to Ison *et al.*

It is respectfully requested that the rejection of claims 1 – 33 under 35 USC §102(a) and (b) as anticipated by, or in the alternative, under 35 USC §103(a) as obvious over U.S. Patent No. 6,013,591 to Ying *et al.*, U.S. Patent No. 5,149,368 to Liu *et al.*, U.S. Patent Nos. 5,522,893 or 5,954,867 to Chow *et al.*, U.S. Patent Nos. 5,885,540, 5,571,493, 5,569,540, 5,709,742, or 5,683,667 to Fulmer *et al.*, or U.S. Patent Nos. 5,496,399 or 5,683,496 to Ison *et al.*, be reconsidered in view of the amendments to the claims and upon consideration of the reasons discussed below and be withdrawn.

Claim 1 has been amended to describe the cement powder as containing tricalcium phosphate nanoparticles that include a sulfate salt in an amount sufficient to prevent at least a portion of the tricalcium phosphate from forming hydroxyapatite. Claim 15, drawn to a cement paste, and claim 28, drawn to a biocompatible cured cement, have also been amended to include this feature.

New claims 62, 68 and 72, are similar to claims 1, 15 and 28, respectively, except that the feature describing the inclusion of the sulfate salt has been replaced with the requirement that the cement powder or paste cures to form a biocompatible cured cement having a compressive strength that is greater than 65 MPa.

It is believed that these independent claims, and all claims that depend therefrom, are patentable over the cited references for the reasons that follow:

U.S. Patent No. 6,013,591 to Ying *et al.*

The Ying *et al.* patent describes methods for producing nanocrystalline apatites, and in particular, hydroxyapatites. (See the Abstract). Unlike the reactive TCP nanoparticles of the present invention, the particles made by Ying *et al.* would not be expected to be reactive to form a cementous material, because they are highly crystalline and hydroxyapatite is known to be one of the least soluble forms of calcium phosphate. Furthermore, there is no indication that the nanocrystalline apatites contain any amount of a sulfate salt, as required by each of the present claims 1 - 33. Rather than participating in a cement-curing reaction, as do the instant reactive nanoparticles, the particles of Ying *et al.* are often densified and are formed into useful products by sintering. See, *e.g.*, col. 10, lines 17 – 29. Although the particles are stated to be useful in cements (col. 10, lines 30 – 50), the hydroxyapatite particles appear to act as a dense biocompatible filler, rather than a reactant in a cement-curing reaction. (See, *e.g.*, col.

35, lines 31 – 67.) Moreover, modification of the methods and compositions of Ying *et al.* to impede the formation of hydroxyapatite, as is required in present claims 1 - 33, would appear to be contrary to the purposes that Ying *et al.* teach.

Because of the non-reactivity of the Ying *et al.* particles, there is no indication that the nanoparticles of Ying *et al.* could form a cured biocompatible cement having a compressive strength of greater than 65 MPa, as required in claims 62 – 75.

Accordingly, it is believed that the Ying *et al.* patent, alone or in combination with any other reference, cannot anticipate or make obvious the cement powders, pastes, and cured cements of the present claims.

U.S. Patent No. 5,149,368 to Liu *et al.*

In this patent, Liu *et al.* teach the formation of a cement powder with tetracalcium phosphate, or a mixture of tetracalcium phosphate and o-tricalcium phosphate. There appears to be no recognition of the desirability of maintaining at least a portion of the tricalcium phosphate in non-hydroxyapatite form, and there is no indication that a sulfate salt is used during the formation of the phosphate particles. Accordingly, there is no teaching or suggestion of the presence of a sufficient amount of sulfate to maintain at least a portion of the TCP in non-hydroxyapatite form, as is required in claims 1 – 33.

The Liu *et al.* patent describes methods for the production of calcium phosphate cements, but does not report the compressive strength of any of the compositions. In order to compare the compressive strength of the Liu *et al.* cements with the biocompatible cements of the present invention, Dr. Genge (an inventor of the present invention) has performed tests that permit the direct comparison of the compressive strength of cements made according to the methods described by Liu *et al.* with the compressive strength of cements made according to the novel methods described in the present application. Dr. Genge's results are shown in the Declaration under 37 C.F.R. §1.132 that is enclosed with this Response.

In his Declaration, Dr. Genge describes the production of cements according to methods described in the Liu *et al.* patent. The compressive strength at 24 hours of those cements is shown to range from about 1.4 MPa to about 11.6 MPa. In comparison, the compressive strength of an embodiment of a cement of the present invention is over 90 MPa well before 24 hours. Accordingly, it is maintained that the compositions taught by Liu *et al.* cannot teach or suggest the cement powders, pastes

and cured cements that are described in claims 62, 68, 72, and claims that depend therefrom, each of which describes a composition that contains novel reactive tricalcium phosphate nanoparticles that can form a cement that cures to form a biocompatible cured cement having a compressive strength that is greater than 65 MPa.

It is respectfully requested, therefore, that the rejection of the present claims over U.S. Patent No. 5,149,368 to Liu *et al.* be reconsidered and withdrawn.

U.S. Patent Nos. 5,522,893 or 5,954,867 to Chow *et al.*

U.S. Patent No. 5,522,893 to Chow *et al.* describes a calcium-phosphate composition that comprises tetracalcium phosphate and at least one other sparingly soluble calcium phosphate compound, wherein the tetracalcium phosphate is prepared from a starting mixture that has a calcium-to-phosphorous of less than 2, but greater than 1.67. The reference does not show the presence of a sulfate salt in the cement powder, paste or cured cement, and no sulfate salt is mentioned as being present in the solutions that are used for the formation of any of the calcium phosphates that are used in the compositions. Accordingly, it is maintained that this references cannot teach or suggest the reactive TCP nanoparticles of the present invention, which are required in claims 1 – 33 to contain a suitable amount of a sulfate salt.

Furthermore, the cements that are produced by the method taught by the `893 patent do not provide a compressive strength of greater than 65 MPa, as required by each of present claims 62 – 75. For example, in Table III, col. 11 – 12, of the `893 patent, the compressive strength of the improved CPC composition (the subject of the `893 patent) is shown as 64.8 MPa.

It is maintained, therefore, that the `893 patent cannot teach or suggest the present invention, as described in claims 1 – 33 and 62 – 75.

U.S. Patent No. 5,954,867 to Chow *et al.* describes the production of an hydroxyapatite cement by a method that accelerates hydroxyapatite formation in slurry systems that do not contain tetracalcium phosphate. See col. 6, lines 50 – 57. In the method described, this is accomplished by maintaining a high phosphate concentration (0.2 mol/L or higher), or by raising the solution pH to about 12.5 or above to provide a high degree of supersaturation with respect to hydroxyapatite. The formation of the calcium phosphate cement powder, as described at col. 8, lines 25 – 34, is accomplished by mixing a calcium phosphate salt that is free of tetracalcium phosphate,

with an additional source of calcium No sulfate salt is present, as is required in the present claims 1 – 33, and the presence of a sulfate salt, which is included in the present invention in order to impede the formation of hydroxyapatite, would not be suggested by the teachings of Chow *et al.*, which are directed to methods that accelerate hydroxyapatite formation, rather than to impede it. Moreover, Table II at col. 9 – 10 of the Chow *et al.* patent show the diametral tensile strength (DTS) of their products to run from less than 1 to about 7.5 MPa. Although the relationship between DTS and compressive strength is not shown in this patent, it is believed to be probable that the compressive strength of the cements shown in Table II are significantly less than 65 MPa. This is because Chow *et al.* showed that similar cements having DTS values of 13.1 MPa had compressive strength of 64.8 MPa, and those having DTS values of 6.9 MPa had a compressive strength of 36 MPa. (See, *e.g.*, Table III, at col. 11, bottom, and extending to col. 12, of U.S. Patent 5,522,893, as described above.) Accordingly, one would expect the compressive strength of the compositions of Patent No. 5,954,867 to be somewhat over 36 MPa, but significantly less than 64.8 MPa. Accordingly, none of the compositions described in the present Chow *et al.* patent show a compressive strength of greater than 65 MPa, as required in each of claims 62 – 75.

Therefore, it is maintained that U.S. Patent 5,954,867, does not teach or suggest the cement powders, pastes, or cured cements of the present invention.

U.S. Patent Nos. 5,885,540, 5,571,493, 5,569,540, 5,709,742, or 5,683,667 to Fulmer *et al.*

Each of the Fulmer *et al.* patents that are cited are divisionals or continuations of Application Ser. No. 334,519, which issued as U.S. Patent No. 5,569,442. It is presumed, therefore, that the same subject matter is disclosed in the specification of each patent.

The Fulmer *et al.* patents describe methods of making a reactive tricalcium phosphate by heating a source of tricalcium phosphate to a certain temperature to form uniform alpha-tricalcium phosphate, rapidly cooling, and, optionally, milling, to form reactive alpha-tricalcium phosphate particles (`442, `667, and `540); a cement formulation that includes a reactive tricalcium phosphate, an additional source of calcium, and partially neutralized phosphoric acid (`742); and a method of preparing an apatitic product suitable for use in bone repair (`493).

The compressive strength of cement that is produced from the material of Fulmer *et al.* is reported in Table 1 (*e.g.*, at col. 9 of the `540 patent) to range from about 20 to about 44 MPa, and, again, in Table 3 (col. 12 of the `540 patent) to range from about 12 to about 62 MPa. Nowhere is it shown that the compressive strength of cement produced from the Fulmer *et al.* materials can be greater than 65 MPa, as required by present claims 62 – 75.

Moreover, as indicated in Examples 1 – 3 of the `540 patent, no sulfate salt is used in the production of the reactive nanoparticles of Fulmer *et al.* Therefore, it is maintained that none of the Fulmer *et al.* patents teach or suggest the cement powder, paste, or cured cement of present claims 1 – 33 and 62 – 75.

U.S. Patent Nos. 5,496,399 or 5,683,496 to Ison *et al.*

U.S. Patent No. 5,683,496 was issued from an application that was filed as a divisional from U.S. Patent Application No. 294,325, which resulted in the issuance of U.S. Patent No. 5,496,399. Accordingly, the specifications of both of these references should be identical.

The Ison *et al.* patents describe a storage-stable cement composition and a method for its production, where the composition includes dry basic calcium source particles at least partially coated with a partially neutralized acidic calcium phosphate, where the dry particles have been produced by mixing an acidic phosphate source (*e.g.*, tetracalcium phosphate, or alpha-tricalcium phosphate) with a basic calcium source (*e.g.*, monobasic calcium phosphate monohydrate) in an aqueous solvent, and then stopping the reaction that occurs between the basic calcium source and the acidic phosphate source prior to its completion by removing the water. The compressive strength of the cement that resulted from the composition was measured and reported in Example 1 (col. 10, lines 29 – 30 of the `399 patent) as 5 MPa; in Example 2 as 48.5 MPa (col. 11, lines 1, 2 of the `399 patent), and 33 MPa (col. 11, lines 16, 17 of the `399 patent). It is maintained, therefore, that the cited patents of Ison *et al.* do not teach or suggest a cement powder or paste that cures into a cement composition having a compressive strength of greater than 65 MPa, as is required for each of the present claims 62 – 75.

Furthermore, it is maintained that there is no teaching in the cited Ison *et al.* patents of the presence or use of a sulfate salt in the production of the reactive calcium

phosphate particles. It is believed, therefore, that the Ison *et al.* patents cannot teach or suggest a powder, paste or cured cement that contains a sulfate salt, as is required by each of present claims 1 – 33.

For the reasons discussed above, it is maintained that claims 1 – 33 and 62 – 75, as presently amended, are not taught or suggested by any of the prior art patents that have been cited, either alone or in combination. It is respectfully requested, therefore, that the present ground of rejection be reconsidered and withdrawn.

Rejection of claims 1 – 33 under 35 USC §112, second paragraph, as failing to set forth the subject matter which applicants regard as their invention:

The Office objected to the terms "and other ingredients" as being indefinite, because the identity of the "other materials" was not particularly pointed out and distinctly claimed. The claims have been amended by deleting the terms that were objected to. It is believed that the terms are not necessary for the description of the subject matter that is being claimed.

The Office objected to the use of the term "cementous". Accordingly, the term "cementous" has been deleted from the claims.

In the claims in which the terms appear, "Group IA" and "Group IIA" have been capitalized.

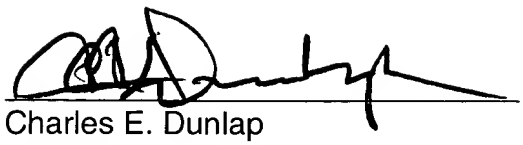
The Office objected to the use of the terms "wherein the bioactive agent comprises a growth factor" in claim 27, as being indefinite. Accordingly, the terms have been amended to read: "wherein the bioactive agent is a growth factor".

Request for reconsideration:

It is respectfully requested that the amendments that are requested above be entered into the case and that the claims be examined in view of the present amendments and be found to be allowable. If one or all of the claims are deemed to not be allowable, the Examiner is invited to call the undersigned attorney at the number given below for resolution of any remaining issues.

Respectfully requested,
NELSON MULLINS RILEY & SCARBOROUGH

Sept. 12, 2003
Date



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